Bushehr University of Medical Sciences
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Final Report of Research Project (Thesis of Medical Degree)

Comparison of efficacy and tolerability of Duloxetine vs. Gabapentin in treatment of diabetic peripheral neuropathic pain

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In the name of

Allah

Special thanks to:

My dear husband

&

My advisors

ABSTRACT

Introduction: Diabetic peripheral neuropathy (DPN) is one of the most common symptomatic, long-term complications in patients with both type 1 and type 2 diabetes mellitus, and most common and most debilitating of the diabetic neuropathies.

Duloxetine, a selective serotonin norepinephrine reuptake inhibitor (SNRI), is effective for the treatment of painful diabetic polyneuropathy. The most common reported side effects of duloxetine are nausea, somnolence, dizziness, decreased appetite, and constipation.

Gabapentin is an anticonvulsant effective in peripheral diabetic neuropathic pain. Side effects include dizziness, sedation and weight gain.

Methods: We selected 60 diabetic patients, with peripheral diabetic neuropathic pain, including of 33 men (mean age=43 years), and 27 women (mean age=42 years). Of these 60 patients 43 patients had been treated with gabapentin and had an inadequate response after at least 3months of treatment, and 17 patients had been complicated with side effects before reaching full dose of Gabapentin. We started Duloxetine 60mg once daily and evaluated the patients' pain improvement after 3months.

Results: Mean pain score was 6.21 before starting Gabapentin, 5.28 after 3months treatment with Gabapentin, and 4.61 after 3months treatment with Duloxetine (P value=0.000). Checking HbA1C before and after treatment with Duloxetine showed

significant decrease, but checking blood pressure before and after treatment with Duloxetine showed no significant change.

Conclusion: Duloxetine with dose of 60 mg once daily is effective and tolerable for diabetic patients with peripheral diabetic neuropathic pain.

Key Words: Diabetic peripheral neuropathic pain; Diabetes; Duloxetine; selective serotonin norepinephrine reuptake inhibitor

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INTRODUCTION

DIABETES MELITUS

Diabetes mellitus is one of the most common metabolic diseases and affects over 18 million people in the United States alone. Individuals with long-standing disease are at increased risk for numerous medical complications associated with significant morbidity and mortality.

Diabetic complications can be classified broadly as microvascular or macrovascular disease.

Microvascular complications include neuropathy (nerve damage), nephropathy (kidney disease) and vision disorders (eg retinopathy, glaucoma, cataract and corneal disease). Macrovascular complications include heart disease, stroke and peripheral vascular disease (which can lead to ulcers, gangrene and amputation).

Other complications of diabetes include infections, metabolic difficulties, impotence, autonomic neuropathy and pregnancy problems.

DIABETIC NEUROPATHY

Neuropathy is the most common diabetic microvascular complication affecting up to 6-7% of general population and 15-20% of all individuals with diabetes type 1 and

type 2 [1]. Diabetic neuropathy is a symmetrical peripheral polyneuropathy that results from nerve damage after prolonged periods of suboptimal glycemic control and is classified based on the location of the nerves affected; These include:

1. Peripheral: toes, feet, legs, hands, and arms;
2. Autonomic: heart and vasculature, digestive tract, urinary tract, sex organs, sweat glands, and the eyes;
3. Proximal: thighs, hips, and buttocks;
4. Focal: eyes, facial muscles, ears, pelvis and lower back, thigh, and abdomen.

Diabetic peripheral neuropathy (DPN) is one of the most common symptomatic, long-term complications in patients with both type 1 and type 2 diabetes mellitus [2], and most common and most debilitating of the diabetic neuropathies. At initial diagnosis, 7.5% of patients will already experience DPN pain, and approximately 45% will be afflicted with this complication after 25 years [3-5].

Peripheral neuropathies manifest with painful or painless symptoms, and many diabetic patients experience both [6]. Approximately 10%–20% develop the painful version of this disorder. Peripheral neuropathic pain occurs when a lesion or dysfunction affects the peripheral nervous system [7].

PATHOPHYSIOLOGY:

Painful diabetic neuropathy most likely occurs as a result of metabolic changes in the neurons as well as hyperglycemia-associated microvascular damage that lead to

abnormal signaling from the peripheral nociceptor that is perceived in the brain as pain. Although the exact pathophysiologic mechanism of diabetic neuropathy is not clearly delineated, it is widely recognized that disinhibition and imbalance of 5-hydroxytryptamine (5-HT) and norepinephrine (NE) in endogenous pain inhibitory pathways could contribute to persistent pain mechanisms.

Substantial morbidity is associated with diabetic peripheral neuropathy, which is the leading risk factor for diabetic foot complications and nontraumatic amputations. Though these late complications frequently occur in the insensate foot, symptomatic DPN also significantly impacts quality of life [8,9].

CLINICAL MANIFESTATIONS:

Diabetic polyneuropathy is primarily a symmetrical sensory neuropathy, initially affecting the distal lower extremities. With disease progression, sensory loss ascends and, when reaching approximately mid-calf, appears in the hands.

SIGNS AND SYMPTOMS:

The earliest signs of diabetic neuropathy probably reflect the gradual loss of integrity of both large myelinated and small myelinated and unmyelinated nerve fibers:

- Loss of vibratory sensation and altered proprioception reflect large- fiber loss.
- Impairment of pain, light touch and temperature is secondary to loss of small fibers.

Decreased or absent ankle reflexes occur early in the disease, while more widespread loss of reflexes and motor weakness are late findings.[10,11]

DIAGNOSIS:

It is important to confirm that the pain is due to diabetic polyneuropathy, and nondiabetic etiologies should be excluded.

The onset of severe pain in the feet and lower limbs can be very distressing and disabling. Neuropathic pain should be distinguished from nociceptive pain which is a consequence of trauma, injury, or inflammation. A disc lesion should be considered if the pain has developed in relation to recent trauma or its onset is abrupt. In addition, pain due to disc disease is more often unilateral than pain related to peripheral neuropathy.

In the absence of these features, the differential diagnosis is neuropathy or peripheral vascular disease. The physical examination may be helpful (decreased sensation or loss of deep tendon reflexes), but these signs of neuropathy do not necessarily mean that the pain is due to the neuropathy. Several clues that the patient has neuropathic pain are the location of pain (feet more than calves), the quality of the pain, and the timing of pain (present at rest, improves with walking). Each of these features is different from those of the pain due to ischemic vascular disease.

Polyneuropathy should be diagnosed on the basis of both clinical (pain and paresthesia, loss of vibratory and light touch, and reduced or absent ankle reflexes) and [12].

TREATMENT:

There are three main elements in the treatment regimen:

Glycemic control: The first and most important treatment for all DPNP patients is maintaining glucose concentrations within the normal range. Tight glycemic control can prevent progression of diabetic neuropathy [13, 14], and multiple studies have shown that improving glycemic control can reduce pain in DPNP patients [15-17]. However, DPNP commonly occurs even in patients with good glycemic control [18], and pharmacologic treatments directed at pain are often necessary to manage DPNP.

Foot care: Patients need to inspect their feet for the presence of dry or cracking skin, fissures, plantar callus formation, and signs of early infection between the toes and around the toe nails. Regular foot examinations by the physician to detect early neuropathy are also an essential component of the treatment of diabetic patients.

Once a patient has diabetic neuropathy, foot care is even more important to prevent ulceration, infection, and amputation [18].

Treatment of pain: Treatments that may be beneficial for painful diabetic neuropathy include a number of antidepressants (eg, amitriptyline, duloxetine, venlafaxine) and anticonvulsants (eg, pregabalin, sodium valproate) as well as capsaicin cream, lidocaine patch, alpha-lipoic acid, isosorbide dinitrate topical spray, and transcutaneous electrical nerve stimulation.

Antidepressants — tricyclic drugs (mainly amitriptyline) and the antidepressants duloxetine and venlafaxine are beneficial for reducing pain associated with diabetic neuropathy.

Tricyclic drugs —Several tricyclic antidepressant drugs (but not selective serotonin reuptake inhibitors) improve symptoms in patients with painful diabetic neuropathy [19-22].

Tricyclics may act by altering the central perception of pain. The therapeutic effect usually occurs sooner (within six weeks) and at lower doses than is typical when these drugs are given for the treatment of depression. Common side-effects of tricyclic antidepressants include dry mouth and somnolence [20].

Duloxetine — Duloxetine, a dual serotonin and norepinephrine reuptake inhibitor, is effective for the treatment of painful diabetic polyneuropathy [23].

The main uses of duloxetine are in major depressive disorder, general anxiety disorder, stress urinary incontinence, painful peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain associated with osteoarthritis and chronic lower back pain. It is being studied for various other indications.

Duloxetine is thought to reduce the perception of pain by increasing the activity of descending pain pathways that dampen pain signals arising from the periphery and being relayed through the spinal cord dorsal horn [24].

duloxetine may be a good choice for DPNP patients with co-existing mood disorders and/or chronic musculoskeletal pain.

In previous studies duloxetine has showed rapid onset of action and sustained benefit, and it was also effective in relieving pain at night and resulted in modest increases in fasting plasma glucose. Effective dose is 60-120mg daily.

Duloxetine is not effective for the numbness or tingling, nor for the other complications of diabetes. It reduces the pain without treating the underlying nerve damage.

The most common reported side effects of duloxetine are nausea, somnolence, dizziness, decreased appetite, and constipation. Hot flashes and erectile dysfunction are also reported infrequently.

Duloxetine should not be taken with other serotonin or norepinephrine uptake inhibitors but can be combined with anticonvulsant therapy.

Venlafaxine —is the other antidepressant effective in peripheral diabetic neuropathic pain, Nausea and somnolence are the most common side effects.

Anticonvulsants — Both newer (pregabalin) and older (valproate) anticonvulsants may be useful for treating painful DPN.

1. **Pregabalin** — Pregabalin is an alpha2-delta ligand that is structurally related to gabapentin but without known activity at GABA or benzodiazepine receptors [25]. It appears to act as a presynaptic inhibitor of the release of excitatory neurotransmitters including glutamate, substance P, and calcitonin gene-related peptide (CGRP) [26,27].The most common adverse events are dizziness, somnolence, peripheral edema, weight gain, blurred vision, sedation, and confusion [28].